REMARKS

Claims 5-7 and 49-65 are pending in the Application. Claims 1-4 and 8-48 have been cancelled. Claims 57-66 have been renumbered 56-65 in the Office Action. The Examiner has withdrawn claims 56-59 from consideration and Applicants will cancel these claims, deemed by the Examiner to be drawn to a non-elected group, upon the filing of a divisional application thereon. Claims 5-7, 49-55, and 60-65 are rejected under 35 U.S.C. § 112, second paragraph and claims 5-7, 49-56 (thought to be 55) and 61-65 are rejected under 35 U.S.C. § 112, first paragraph. Pending claims are also rejected under 35 U.S.C. § 102(b) as being anticipated by a number of references. Applicants respectfully request reconsideration of pending claims and entry of the amended and new claims in view of the following remarks.

Elections / Restrictions

Regarding newly added claims 49-65 from paper No. 8, the Examiner has rejoined claims 49-55 and 65 with elected claims 5-7 "because they are directed to a eukaryotic virus pseudo-nucleocapsid formed by a cell free in vitro self-assembly system." The Examiner did not rejoin claims 57-61 with claims 5-7, "because they are drawn to a virus pseudo-nucleocapsid with different structure characteristics and produced by using a vector in cell culture system" and "should be restricted to another group." Claims 5-7, 49-55 and 60-65 are to be considered before the Examiner. Applicants will cancel claims 56-59 upon the filing of a divisional application.

Claim Rejections under 35 U.S.C. § 112, second paragraph

Claims 5-7, 49-55, and 60-65 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite and for failing to particularly point out and distinctly claim the subject matter that the applicant regards as the invention. Applicants respectfully submit amended claims 5-6, 49, 51, 53, 55, and 60, no longer believed indefinite or failing to particularly point out and distinctly claim the subject matter of the invention. Applicants also respectfully request claims 7, 52, 54, and 61-65 be cancelled. Claims 5-6, 49, 51, 53, 55, and 60 have been amended to address Office Action rejections as discussed below.

Claim 5 is said to be "unclear for recitation that the claimed virus pseudo-nucleocapsid comprising at least more a portion of a viral capsid polypeptide and a polynucleotide. First, the

phrase 'comprising at least' used here is a relative word, which fails to define the structural characteristics of the claimed product. Moreover, the metes and bounds of a portion of a viral capsid polypeptide and a polynucleotide are not defined." (Emphasis in original). Applicants have amended claim 5 to make clear the recitation of a eukaryotic virus pseudo-nucleocapsid as "consisting essentially of" rather than "comprising" and have further defined the metes and bounds of a viral capsid polypeptide as one that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein." As amended, claim 5 is no longer unclear and now defines the structural characteristics of the claimed product and, thus, no longer affects claims 6-7, 49-52 and 55. As such, Applicants respectfully request that the rejection to amended claim 5 be withdrawn.

Claim 49, 51, 53, and 55 are said to be "indefinite for using a relative word of 'comprising,' which fails to define what the precise structure or component of each element contained in the claimed virus pseudo-nucleocapsid." Applicants have amended claims 49, 51, 53, and 55 to recite the definite word "is" (claims 49, 51), "consists essentially of" (claim 53), or "from the group consisting essentially of" (claim 55) rather than "comprising." As amended, claims 49, 51, 53, and 55 are no longer indefinite for using a relative word of "comprising." As such, Applicants respectfully request that rejections to amended claims 49, 51, 53, and 55 be withdrawn.

Claim 51 is said to be "vague and indefinite in that the metes and bounds of a recombinant polypeptide are not defined." Applicants have amended claim 5 from which claim 51 depends to define the metes and bounds of a viral capsid polypeptide as one that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein." As such, the metes and bounds of a recombinant polypeptide of claim 51 are now defined. Applicants, thus, respectfully request that the rejection to amended claim 51 be withdrawn.

Applicants respectfully submit new claims 66-74 for consideration and allowance. The new claims find support throughout the Specification, examples of which are shown below.

> More specifically, an *E. coli* pET30 vector (Novagen) encoding the HCV core protein was constructed using the polymerase chain reaction (PCR) methods from a template cDNA encoding capsid protein from HCV (strain AG94, genotype 1a). [page 39, ll. 13-17]

> Urea denatured core protein, purified from the insoluble fraction of the bacterial cell lysate, may be refolded by dialysing against physiological buffers. [page 41, ll. 3-5]
>
> Figure 1a-e shows the amino-acid sequences of these five variants: the full-length core protein (residues 1-191, 20.7 kD, SEG. ID. No.: 1), and carboxy terminus truncated variants Δ12 (residues 1-179, 19.6 kD, SEQ ID NO.: 1), and Δ67 (residues 1-124, 13.7 kD). Truncated core variants were chosen to either eliminate the long hydrophobic stretches of the protein (constructs Δ67) or to optimize protein expression (construct Δ12 and Δ67). [page 40, ll. 9-12, emphasis added]
>
> Nucleocapsid pseudo-particles are generated by mixing purified recombinant core protein or core protein truncation variants with RNA under defined conditions. [page 42, ll. 20-21 and page 43, l. 1]
>
> Electron microscopy of negative stained preparations comprising the mixture of HCVC124 capsid protein and tRNA showed the formation of spheroid LSVL particles (data not shown). [page 43, ll. 13-16]
>
> In one example, purified recombinant HCV capsid protein (HCVC124) was diluted in assembly buffer (100 mM KAcetate, 1.7 mM MgAcetate, 25 mM HEPES pH 7.4, 5 mM DTT) to a final concentration of approximately 1mg/ml 0r 0.1mM. Oligonucleotides (e.g., $tRNA_{Phe}$, SIGMA) are resuspended in assembly buffer to a final relative ratio of 1/10 nucleotide to protein concentration. These amounts were found to be an example of an effective protein polynucleotide ratio. [pg. 43, ll. 1-10, emphasis added]

In light of the above remarks, Applicants respectfully request entry and allowance of amended claims 5-6, 49, 51, 53, 55, and 60 and new claims 66-74. In addition, it is requested that claims 7, 52, 54, and 61-65 be cancelled.

Claim Rejections under 35 U.S.C. § 112, first paragraph

Claims 5-7, 49-56 and 61-65 are rejected under 35 U.S.C. § 112, first paragraph, "because the specification, while being enabled for having a HCV pseudo-nucleocapsid made by incubating the mixture of HCV core protein encoded by SEQ ID NO:1 and tRNA in an in vitro array, does not reasonably provide enablement for having any or eukaryotic virus pseudo-nucelocapsid comprising any or all a portion of viral capsid polypeptide and a polynucleotide formed in any or all in vitro system. . . . it must be considered that the skilled artisan would have had to conduct undue and excessive experimentation in order to practice the claimed invention." Applicants respectfully submit amended claims 5-6, 49, 51, 53, 55, and 60 that have been

amended to address Office Action rejections as discussed below. In addition, applicants respectfully request cancellation of claims 7, 52, 54, and 61-65.

Claim 5 had been amended to provide the metes and bounds for the viral capsid polypeptide that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein" and for the formation of the eukaryotic virus pseudo-nucleocapsid "after which no additional purification step is required." As such, amended claim 5 is enabled within the scope of the specification and one of skill in the relevant art would be able to make and use the claimed invention without undue experimentation.

Claims 6 depends from amended claim 5 that now includes the metes and bounds for the viral capsid polypeptide that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein" and is further amended to include additional metes and bounds for the viral capsid polypeptide that is "a homologous sequence of a core protein from a member of the *Flaviviridae* family." As such, amended claim 6 is enabled within the scope of the specification and one of skill in the relevant art would be able to make and use the claimed invention without undue experimentation.

Claim 49 depends from amended claim 5 that now includes the metes and bounds for the viral capsid polypeptide that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein" and is further amended to include the metes and bounds for tRNA "of at least 10 nucleotides." As such, amended claim 49 is enabled within the scope of the specification and one of skill in the relevant art would be able to make and use the claimed invention without undue experimentation.

Claim 50 depends from amended claim 5 that now includes the metes and bounds for the viral capsid polypeptide that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein." As such, claim 50 as it depends from amended claim 5 is enabled within the scope of the specification and one of skill in the relevant art would be able to make and use the invention without undue experimentation.

Claim 51 depends from amended claim 5 that now includes the metes and bounds for the viral capsid polypeptide that "comprises at least the first 124 amino-terminal residues of a

hepatitis C virus core protein" and is further amended to include the metes and bounds for said viral capsid polypeptide that "is a recombinant polypeptide." As such, amended claim 51 is enabled within the scope of the specification and one of skill in the relevant art would be able to make and use the claimed invention without undue experimentation.

Claim 53 depends from amended claim 5 that now includes the metes and bounds for the viral capsid polypeptide that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein" and is further amended such that "said viral capsid polypeptide consists essentially of SEQ ID NO.: 1." As such, amended claim 53 is enabled within the scope of the specification and one of skill in the relevant art would be able to make and use the claimed invention without undue experimentation.

Claim 55 depends from amended claim 5 that now includes the metes and bounds for the viral capsid polypeptide that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein" and is further amended such that "said polynucleotide is from the group consisting essentially of hepatitis C virus genome and member of the *Flaviviridae* family." As such, amended claim 55 is enabled within the scope of the specification and one of skill in the relevant art would be able to make and use the claimed invention without undue experimentation.

Claim 60 depends from amended claim 5 that now includes the metes and bounds for the viral capsid polypeptide that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein" and is further amended such that "said viral capsid polypeptide is formed by adding to a cell-free in vitro system a recombinant DNA consisting essentially of at least the first 124 amino-terminal residues of the hepatitis C virus core protein or a homologous sequence of a core protein from a member of the *Flaviviridae* family." As such, amended claim 60 is enabled within the scope of the specification and one of skill in the relevant art would be able to make and use the claimed invention without undue experimentation.

In light of the above amendments and remarks, Applicants respectfully request entry and allowance of amended claims 5-6, 49, 51, 53, 55, and 60, while cancellation of claims 7, 52, 54, and 61-65 is requested.

Claim Rejections under 35 U.S.C. § 102(b)

In order for a rejection under 35 U.S.C. § 102(b) to be proper, the cited reference must teach each and every aspect of the claimed invention either explicitly or impliedly. See MPEP § 2131. A single reference must identically disclose every element of the claimed invention. *Corning Glass Works v. Sumitomo Electric*, 9 U.S.P.Q. 2d 1962, 1965 (Fed. Cir. 1989). A reference that excludes a claimed element, no matter how insubstantial or obvious, is enough to negate anticipation. *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. 193, 198 (Fed. Cir. 1983). As elaborated in *Richardson v. Suzuki Motor Co.* "[t]he identical invention must be shown in as complete detail as is contained in the claim." 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1987).

Rejection of Claims 5, 50, 51, and 61-63 under 35 U.S.C. § 102(b)

Claims 5, 50, 51, and 61-63 are rejected under 35 U.S.C. § 102(b) as being anticipated by Spearman et al. (J. Virol. 1996, Vol. 70, pp. 8187-8194) and Lingappa et al (J. Cell Biology. 1994, Vol. 125, pp. 99-111). Applicants submit amended claims 5 and 51 and claim 50 that each depend from amended claim 5, and request cancellation of claims 61-63. Because claim 50 and amended claims 5 and 51 and every limitation thereof are neither identical nor anticipated by Spearman et al. or Lingappa et al., Applicants respectfully request that the rejections to claim 50 and amended claims 5 and 51 under 35 U.S.C. § 102(b) be withdrawn.

Claim 5 has been amended to provide the metes and bounds for the viral capsid polypeptide that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein," and for the formation of the eukaryotic virus pseudo-nucleocapsid "after which no additional purification step is required." Neither Lingappa et al. nor Spearman et al. disclose either implicitly or explicitly eukaryotic virus pseudo-nucleocapsid formation with "at least the first 124 amino-terminal residues of a hepatitis C virus." Nor do Lingappa et al. or Spearman et al. disclose the formation of pseudo-nucleocapsids "after which no additional purification step is required." Importantly, neither Lingappa nor Spearman teach nucelocapsid formation with "at least the first 124 amino-terminal residues of a hepatitis C virus core protein; and a polynucleotide." Instead, Lingappa et al. teaches the synthesis of hepatitis B core polypeptides (at least 21 kD) that can form "mature core particles" requiring either "sucrose, CsCl, or glycerol fractionation" prior to analysis. (See Materials and Methods, pg. 100-101 and Results, pg. 101,

col. 1, emphasis added) Importantly, Lingappa does not teach polynucleotides with core particles nor does the reference discuss any type of association between "mature core particles" and polynucleotides. Spearman et al. teaches the synthesis of the "Gag polyprotein of human immunodeficiency virus (HIV)" able to "direct particle assembly events when expressed within tissue culture cells." (See Abstract) Furthermore, Spearman et al. teaches that while Gag proteins are able to form particles (capsids), the formation products must be analyzed "by equilibrium centrifugation on sucrose gradients." (See pg. 8188, col. 1, last three lines) More importantly, Spearman teaches an incubation step in which particles are digested with RNAse for 1 hour prior to capsid formation analysis, indicating particles lack polynucleotide association. (See pg. 8188, col. 1, second paragraph)

As such, claim 5 and all claims that depend from claim 5, namely claim 50 and amended claim 51, are not anticipated by Lingappa et al. or Spearman et al. Because none of the claims are anticipated by Lingappa et al. or Spearman et al., Applicants respectfully request that the rejection of claim 50 and amended claims 5 and 51 under 35 U.S.C. § 102(b) be withdrawn.

Rejection of Claims 5-7, 49, 51, and 61-63 under 35 U.S.C. § 102(b)

Claims 5-7, 49, 51, and 61-63 are rejected under 35 U.S.C. § 102(b) as being anticipated by Sugrue et al. (J. General Virol. 1997, Vol. 78, pp. 1861-1866). Applicants submit amended claim 5 and amended claims 6, 49 and 51 that depend from amended claim 5, and request cancellation of claims 7 and 61-63. Because amended claims 5, 6, 49 and 51 and every limitation thereof are neither identical nor anticipated by Sugrue et al., Applicants respectfully request that the rejections to amended claims 5-6, 49, and 51 under 35 U.S.C. § 102(b) be withdrawn.

Claim 5 has been amended to provide the metes and bounds for the viral capsid polypeptide that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein" and for the formation of the eukaryotic virus pseudo-nucleocapsid "after which no additional purification step is required." While only the Abstract has been reviewed (reference was not made available to Applicants), the Abstract makes clear that Sugrue et al. does not disclose, either implicitly or explicitly, eukaryotic virus pseudo-nucleocapsid formation with "at least the first 124 amino-terminal residues of a hepatitis C virus." Nor does the reference appear

to disclose the formation of pseudo-nucleocapsids "after which no additional purification step is required." Instead, Sugrue et al. teaches the expression of "cDNA encoding the dengue virus structural proteins in *Pichia pastoris* by chromosomal integration of an expression cassette containing the dengue virus structural genes." (See Abstract) Furthermore, the Abstract teaches that "spherical structures with an average diameter of 30 nm, whose morphology resembles the dengue virions, were observed in the purified fractions using transmission electron microscopy" illustrating that the method of Sugrue et al. requires further purification steps to retrieve "spherical structures" that may resemble "dengue virions." (See Abstract, emphasis added)

As such, claim 5 and all claims that depend from claim 5, namely amended claims 6, 49, and 51, are not anticipated by Sugrue et al. Because none of the claims are not anticipated by Sugrue et al., Applicants respectfully request that the rejection of amended claims 5-6, 49, and 51under 35 U.S.C. § 102(b) be withdrawn.

Rejection of Claims** 5-7, 49, 51-55, and 60-65 **under 35 U.S.C. § 102(b)

Claims 5-7, 49, 51-55, and 60-65 are rejected under 35 U.S.C. § 102(b) as being anticipated by Baumert et al. (J. Virol. 1998, Vol. 72, pp. 3827-3836). Applicants submit amended claim 5 and amended claims 6, 49, 51, 53 and 60 that depend from amended claim 5, and request cancellation of claims 7, 52, 54, and 61-65. Because amended claims 5, 6, 49 51, 53 and 60 and every limitation thereof are neither identical nor anticipated by Baumert et al., Applicants respectfully request that the rejections to amended claims 5-6, 49, 51 53, and 60 under 35 U.S.C. § 102(b) be withdrawn.

Claim 5 has been amended to provide the metes and bounds for the viral capsid polypeptide that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein" and for the formation of the eukaryotic virus pseudo-nucleocapsid "after which no additional purification step is required." Baumert et al. does not disclose, either implicitly or explicitly, eukaryotic virus pseudo-nucleocapsid formation with "at least the first 124 amino-terminal residues of a hepatitis C virus." Nor does the reference disclose the formation of pseudo-nucleocapsids "after which no additional purification step is required." Instead, Baumert et al. teaches the "production of HCV structural proteins in insect cells as demonstrated by immunofluorescence analysis of infected insect cells with anti-HCV antibodies (Fig. 2) and

immunoblotting of insect cell lysates (Fig. 3)," where not one but at least two or more HCV structural proteins are co-produced at any one time in vitro and include "the core, E1, E2 and p7 proteins and 21 amino acids of the NS2 protein." (See pg. 3829, col. 2, ll. 8-15) Furthermore, the reference teaches that "viruslike particles appeared not to be released or secreted into the culture medium," such that an additional "purification" step by "sucrose and CsCl gradient centrifugation" is required. (See pg. 3831, col. 1, ll. 36-40)

As such, claim 5 and all claims that depend from claim 5, namely amended claims 6, 49, 51, 53, and 60, are not anticipated by Baumert et al. Because none of the claims are anticipated by Baumert et al., Applicants respectfully request that the rejection of amended claims 5-6, 49, 51, 53, and 60 under 35 U.S.C. § 102(b) be withdrawn.

Rejection of Claims** 5-7, 49, 51, and 60-62 **under 35 U.S.C. § 102(b)

Claims 5-7, 49, 51, and 60-62 are rejected under 35 U.S.C. § 102(b) as being anticipated by Thomsen et al. (J. General Virol. 1992, Vol. 73, pp. 1819-1824). Applicants submit amended claim 5 and amended claims 6, 49, 51, and 60 that depend from amended claim 5, and request cancellation of claims 7 and 61-62. Because amended claims 5, 6, 49, 51 and 60 and every limitation thereof are neither identical nor anticipated by Thomsen et al., Applicants respectfully request that the rejections to amended claims 5, 6, 49, 51 and 60 under 35 U.S.C. § 102(b) be withdrawn.

Claim 5 has been amended to provide the metes and bounds for the viral capsid polypeptide that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein" and for the formation of the eukaryotic virus pseudo-nucleocapsid "after which no additional purification step is required." Thomsen et al. does not disclose, either implicitly or explicitly, eukaryotic virus pseudo-nucleocapsid formation with "at least the first 124 amino-terminal residues of a hepatitis C virus." Nor does the reference disclose the formation of pseudo-nucleocapsids "after which no additional purification step is required." More importantly, Thomsen does not teach nucelocapsid formation with "at least the first 124 amino-terminal residues of a hepatitis C virus core protein; and a polynucleotide." Instead, Thomsen et al. teaches "recombinant baculoviruses that express the FeLV envelope glycoprotein gp85 [*Autographa californica* nuclear polyhedrosis virus (AcNPV)-gp85] and the structural protein,

gag (AcNPVgag)," where "the gag protein is expressed and shed into the medium of infected cells as particles which have a buoyant density on sucrose gradient and appearance by electron microscopy similar to those of authentic FeLV virions." (See Abstract) Further teachings by Thomsen et al include a required additional steps to retrieve particles, namely "hi speed centrifugations" and "fractionations," such that "to test for the assembly of virus-like particles the extracellular fluid of AcNPVgag-infected Sf9 cells was examined by sucrose gradient analysis," (See pg. 1820, col. 2, second paragraph, emphasis added) More importantly, Thomsen et al. does not teach nor does the reference discuss particle association or assembly with any type of polynucleotide.

As such, claim 5 and all claims that depend from claim 5, namely amended claims 6, 49, 51, and 60, are not anticipated by Thomsen et al. Because none of the claims are anticipated by Thomsen et al., Applicants respectfully request that the rejection of amended claims 5, 6, 49, 51 and 60 under 35 U.S.C. § 102(b) be withdrawn.

Rejection of Claims** 5-7, 49, and 51 **under 35 U.S.C. § 102(b)

Claims 5-7, 49, and 51 are rejected under 35 U.S.C. § 102(b) as being anticipated by Yamshchikov et al. (Virol. 1993, Vol. 192, pp. 38-51). Applicants submit amended claim 5 and amended claims 6, 49, and 51 that depend from amended claim 5, and request cancellation of claim 7. Because amended claims 5, 6, 49, and 51 and every limitation thereof are neither identical nor anticipated by Yamshchikov et al., Applicants respectfully request that the rejections to amended claims 5-6, 49, and 51 under 35 U.S.C. § 102(b) be withdrawn.

Claim 5 has been amended to provide the metes and bounds for the viral capsid polypeptide that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein" and for the formation of the eukaryotic virus pseudo-nucleocapsid "after which no additional purification step is required." Yamshchikov et al. does not disclose, either implicitly or explicitly, eukaryotic virus pseudo-nucleocapsid formation with "at least the first 124 amino-terminal residues of a hepatitis C virus." Nor does the reference disclose the formation of pseudo-nucleocapsids "after which no additional purification step is required." Instead, Yamshchikov et al. teaches the "expression of several West Nile flavivirus gene cassettes of different lengths in vaccinia virus expression systems." (See Abstract) Furthermore,

Yamshchikov et al teaches that "virus-like particles were occasionally observed associated with the external cell membrane," but "because such observations were rare, the efficiency of particle formation must be very low." (See pg. 46, col. 2, last paragraph) Rarely, was nucleic acid found to be associated with the particles; the rare nucleic acid was "material with heterogenous mobility." More importantly, Yamshchikov concluded that any nucleic acid found "represent(ed) sheared DNA of the recombinant vaccinia virus" and was not thought to be RNA. (See pg. 47, col. 1, first paragraph)

As such, claim 5 and all claims that depend from claim 5, namely amended claims 6, 49, and 51, are not anticipated by Yamshchikov et al. Because none of the claims are anticipated by Yamshchikov et al., Applicants respectfully request that the rejection of amended claims 5-6, 49, and 51 under 35 U.S.C. § 102(b) be withdrawn.

Rejection of Claims** 5-7, 49-52, 54-55 and 61-65 **under 35 U.S.C. § 102(b)

Claims 5-7, 49-52, 54-55 and 61-65 are rejected under 35 U.S.C. § 102(b) as being anticipated by Yusui et al. (J. Virol. 1998, Vol. 72, pp. 6048-6055) and Liang et al. (WO 98/21338A1). Applicants submit amended claim 5 as well as claim 50 and amended claims 6, 49, 51, 53, 55, and 60 that depend from amended claim 5, and request cancellation of claim 7, 52, 54, 61-65. Because claim 50 and amended claims 5, 6, 49, 51, 53, 55, and 60 and every limitation thereof are neither identical nor anticipated by Yasui et al. or Liang et al., Applicants respectfully request that the rejections to claim 50 and amended claims 5, 6, 49, 51, 53, 55, and 60 under 35 U.S.C. § 102(b) be withdrawn.

Claim 5 has been amended to provide the metes and bounds for the viral capsid polypeptide that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein" and for the formation of the eukaryotic virus pseudo-nucleocapsid "after which no additional purification step is required." Neither Yasui et al. nor Liang et al disclose, either implicitly or explicitly, eukaryotic virus pseudo-nucleocapsid formation with "at least the first 124 amino-terminal residues of a hepatitis C virus." Nor do the references disclose the formation of pseudo-nucleocapsids "after which no additional purification step is required." Instead, Yasui et al. discloses the "maturation and subcellular localization of hepatitis C virus (HCV) core protein" using the entire HCV core protein cDNA (9610 nucleotides) or subsets containing

nucleotides 342-800, 342-870, 342-914, or 342-3745 (See Abstract and Materials and Methods: HCV cDNA contructs). Liang et al teaches "production of enveloped RNA virus-like particles intracellularly in vitro in insect cells using a recombinant baculovirus vector containing a cDNA coding for viral structural proteins," wherein "purification of hepatitis C virus (HCV)-like particles containing HCV core protein, E1 protein and E2 protein is disclosed." (See Abstract and Amended Claims 1 and 2, emphasis added) Particularly, Liang requires "the step of purifying the intracellular virus-like particles from the cultured insect cells." (See Amended Claim 2)

As such, claim 5 and all claims that depend from claim 5, namely claim 50 and amended claims 6, 49, 51, 53, 55, and 60, are not anticipated by Yasui et al. or Liang et al. Because none of the claims are anticipated by Yasui et al. nor Liang et al., Applicants respectfully request that the rejection of claims 5-6, 49-51, 53, 55, and 60 under 35 U.S.C. § 102(b) be withdrawn.

Rejection of Claims** 5-6, 49-51, and 61-63 **under 35 U.S.C. § 102(b)

Claims 5-6, 49-51, and 61-63 are rejected under 35 U.S.C. § 102(b) as being anticipated by Wengler et al. (Virol. 1982, Vol. 118, pp. 401-411). Applicants submit amended claim 5 as well as claim 50 and amended claims 6, 49, and 51 that depend from amended claim 5, and request cancellation of claim 61-63. Because claim 50 and amended claims 5, 6, 49, and 51 and every limitation thereof are neither identical nor anticipated by Wengler et al., Applicants respectfully request that the rejections to claim 50 and amended claims 5-6, 49, and 51 under 35 U.S.C. § 102(b) be withdrawn.

Claim 5 has been amended to provide the metes and bounds for the viral capsid polypeptide that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein" and for the formation of the eukaryotic virus pseudo-nucleocapsid "after which no additional purification step is required." Wengler et al does not disclose, either implicitly or explicitly, eukaryotic virus pseudo-nucleocapsid formation with "at least the first 124 amino-terminal residues of a hepatitis C virus." Nor does the references disclose the formation of pseudo-nucleocapsids "after which no additional purification step is required." Instead, Wengler et al. discloses "a system has been developed that allows the reconstruction of a core-like (CL) ribonucleoprotein (RNP) from Sindbis virus-specific core protein and genomic RNA in vitro."

(See Abstract). Wengler et al teaches "production of enveloped RNA virus-like particles intracellularly in vitro in insect cells using a recombinant baculovirus vector containing a cDNA coding for viral structural proteins," wherein "purification of hepatitis C virus (HCV)-like particles containing HCV core protein, E1 protein and E2 protein is disclosed," where "purification" includes particles "centrifuged to equilibrium in CsCl density gradients." (See Abstract and pg. 403, col. 2, ll. 22-24, emphasis added)

As such, claim 5 and all claims that depend from claim 5, namely claim 50 and amended claims 6, 49, and 51, are not anticipated by Wengler et al. Because the claims are not anticipated by Wengler et al., Applicants respectfully request that the rejection of claim 50 and amended claims 5-6, 49, and 51 under 35 U.S.C. § 102(b) be withdrawn.

Rejection of Claims** 5, 49-51, and 60-63 **under 35 U.S.C. § 102(a)

Claims 5, 49-51, and 60-63 are rejected under 35 U.S.C. § 102(a) as being anticipated by Bothner et al. (Nature Structural Biology, 1999, Vol. 6, pp. 114-116). Applicants submit amended claim 5 as well as claim 50 and amended claims 49, 51, and 60 that depend from amended claim 5, and request cancellation of claim 61-63. Because claim 50 and amended claims 5, 49, 51, and 60 and every limitation thereof are neither identical nor anticipated by Bothner et al., Applicants respectfully request that the rejections to claim 50 and amended claims 5, 49, 51 and 60 under 35 U.S.C. § 102(a) be withdrawn.

Claim 5 has been amended to provide the metes and bounds for the viral capsid polypeptide that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein" and for the formation of the eukaryotic virus pseudo-nucleocapsid "after which no additional purification step is required." Bothner et al does not disclose, either implicitly or explicitly, eukaryotic virus pseudo-nucleocapsid formation with "at least the first 124 amino-terminal residues of a hepatitis C virus." Instead, Bothner et al. discloses "proteolysis and chemical modification experiments were combined with mass spectrometry to investigate viral capsid structural mobility in solution" using "Flock house virus (FHV) capsid . . . composed of 180 copies of a 407 amino acid protein." (See pg. 114, col. 1, first and third paragraph, emphasis added). Furthermore, Bothner et al teaches that an additional step of proteolytic digestion is required prior to analysis of such "viral capsids." (See Methods, pg. 116)

As such, claim 5 and all claims that depend from claim 5, namely claim 50 and amended claims 49, 51 and 60, are not anticipated by Bothner et al. Because none of the claims are anticipated by Bothner et al., Applicants respectfully request that the rejection of claim 50 and amended claims 5, 49, 51 and 60 under 35 U.S.C. § 102(a) be withdrawn.

Rejection of Claims** 5-6, 49-51, and 61-63 **under 35 U.S.C. § 102(a)

Claims 5-6, 49-51, and 61-63 are rejected under 35 U.S.C. § 102(a) as being anticipated by Tellinghuisen et al. (J. Virol. 1999, Vol. 73, pp. 5309-5319). Applicants submit amended claim 5 as well as claim 50 and amended claims 6, 49, and 51 that depend from amended claim 5, and request cancellation of claim 61-63. Because claim 50 and amended claims 5-6, 49, and 51 and every limitation thereof are neither identical nor anticipated by Tellinghuisen et al., Applicants respectfully request that the rejections to claim 50 and amended claims 5-6, 49, and 51 under 35 U.S.C. § 102(a) be withdrawn.

Claim 5 has been amended to provide the metes and bounds for the viral capsid polypeptide that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein" and for the formation of the eukaryotic virus pseudo-nucleocapsid "after which no additional purification step is required." Tellinghuisen et al does not disclose, either implicitly or explicitly, eukaryotic virus pseudo-nucleocapsid formation with "at least the first 124 amino-terminal residues of a hepatitis C virus." Nor does the references disclose the formation of pseudo-nucleocapsids "after which no additional purification step is required." Instead, Tellinghuisen et al. discloses "a heterologous protein expression system, based in *Escherichia coli*, for the expression and purification of large quantities of the SINV CP from amino acid residues 19 to 264." (See pg. 5310, col. 1, ll. 23-25, emphasis added). Specifically, Tellinghuisen et al teaches "A capsid protein starting at residue 19 [CP(19-264)] was fully competent for in vitro assembly, whereas proteins with further N-terminal truncations could not support assembly." (See Abstract, emphasis added) In addition, Tellinghuisen teaches that an additional "sucrose gradient sedimentation" step is required to view the assembled core like particles (CLPs). (See Materials and Methods, Gradient assembly assay)

As such, claim 5 and all claims that depend from claim 5, namely claim 50 and amended claims 6, 49, and 51 are not anticipated by Tellinghuisen et al. Because none of the claims are

anticipated by Tellinghuisen et al., Applicants respectfully request that the rejection of claim 50 and amended claims 5-6, 49, and 51 under 35 U.S.C. § 102(a) be withdrawn.

Rejection of Claims** 5-7, 49-52, 54-55 and 61-65 **under 35 U.S.C. § 102(a)

Claims 5-7, 49-52, 54-55 and 61-65 are rejected under 35 U.S.C. § 102(a) as being anticipated by Falcón et al. (Tissue and Cell. 1999, Vol. 31, pp. 117-125). Applicants submit amended claim 5 as well as claim 50 and amended claims 6, 49, 51, and 55 that depend from amended claim 5, and request cancellation of claims 7, 52, 54, and 61-65. Because claim 50 and amended claims 5-6, 49, 51, and 55 and every limitation thereof are neither identical nor anticipated by Falcón et al., Applicants respectfully request that the rejections to claim 50 and amended claims 5-6, 49, 51, and 55 under 35 U.S.C. § 102(a) be withdrawn.

Claim 5 has been amended to provide the metes and bounds for the viral capsid polypeptide that "comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein" and for the formation of the eukaryotic virus pseudo-nucleocapsid "after which no additional purification step is required." Falcón et al. does not disclose, either implicitly or explicitly, eukaryotic virus pseudo-nucleocapsid formation with "at least the first 124 amino-terminal residues of a hepatitis C virus." Nor does the references disclose the formation of pseudo-nucleocapsids "after which no additional purification step is required." Instead, Falcón et al. discloses, "virus-like particles (VLP)" resulting from expression of "HCV structural proteins" using "a DNA fragment coding for the first 339 amino acids (aa) of the HCV protein," namely the core and E1 proteins. (See pg. 118, Materials and Methods and Fig. 1) Resulting VLPs were only identified intracellularly "along the membrane of the endoplasmic reticulum, but were fundamentally localized in vacuoles, either free or inside autophagic bodies," or as "clustered particles, chains of particles, high-density reticular structures, and crystalloid bodies." (see Abstract) In addition, Falcón et al "argue that membrane components are retained in the architecture of the VLP, conferring to this particle certain heterogeneity." Falcón further teaches two "kinds of particles," that includes "the VLP formed after treatment with NP-40 and the crystal-associated particles." (See pg. Abstract, emphasis added). However, Falcón et al teaches "We failed, however, in demonstrating that the VLP were derived from assembled core proteins (p22 and/or p24). Neither the anti-core Mab-Hep1 or core-reacting human sera were able to

stain the clustered particles." (See pg. 121, col. 1, ll. 25-28, emphasis added, and pg. 122, col. 2) More importantly, Falcón makes no mention of any nucleotide-association with VLPs.

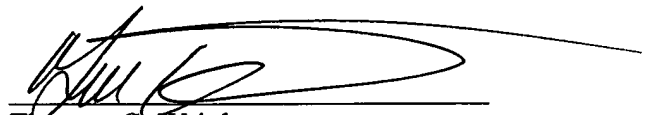
As such, claim 5 and all claims that depend from claim 5, namely claim 50 and amended claims 6, 49, 51, and 55 are not anticipated by Falcón et al. Because none of the claims are anticipated by Falcón et al., Applicants respectfully request that the rejection of claim 50 and amended claims 5-6, 49, 51, and 55 under 35 U.S.C. § 102(a) be withdrawn.

CONCLUSION

In view of the foregoing, it is respectfully submitted that pending claims 5-6, 49, 50-51, 53, 55, and 60 and new claims 66-74 are drawn to novel subject matter, patentably distinct from the cited references. The Examiner is therefore respectfully requested to reconsider and withdraw the outstanding rejections to claims 5-6, 49, 50-51, 53, 55, and 60 and to allow the entry and allowance of new claims 66-74 along with cancellation without prejudice of claims 7, 52, 54, 56-59, and 61-65. Accordingly, a favorable action in the form of an early Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned for any reason that would advance the instant Application to issue. No additional fee is believed to be due with this reply. If any additional fee is due, please charge this fee to our Deposit Account No. 07-0153.

Dated: February 5, 2003

Respectfully submitted,
GARDERE WYNNE SEWELL LLP



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In Re Application:	Stanley J. Watowich, Meghan Kunkel and Marta Lorinczi
Serial No.	09/713,687
Group Art Unit:	1648
Filed:	November 15, 2000
For:	VIRAL PSEUDO-CAPSIDS INCLUDING ASSEMBLY AGONISTS AND ANTAGONISTS

MARKED-UP VERSION OF CLAIMS IN ACCORDANCE WITH 37 C.F.R. § 1.121

5. (AMENDED) A eukaryotic virus pseudo-nucleocapsid [comprising] consisting essentially of:

at least a portion of a viral capsid polypeptide, wherein the viral capsid polypeptide comprises at least the first 124 amino-terminal residues of a hepatitis C virus core protein; and

a polynucleotide, wherein said viral capsid polypeptide and polynucleotide together participate in formation of a generally spheroid pseudo-nucleocapsid in vitro after which no additional purification step is required.

6. (AMENDED) The virus pseudo-nucleocapsid of claim 5, wherein said viral capsid polypeptide is a [flavivirus capsid polypeptide] homologous sequence of a core protein from a member of the *Flaviviridae* family.

49. (AMENDED) The virus pseudo-nucleocapsid of claim 5, wherein said polynucleotide is [comprises] a tRNA of at least 10 nucleotides.

51. (AMENDED) The virus pseudo-nucleocapsid of claim 5, wherein said viral capsid polypeptide is [comprises] a recombinant polypeptide.

53. (AMENDED) The virus pseudo-nucleocapsid of claim 5, wherein said viral capsid polypeptide consists essentially of [comprises] SEQ ID NO.: 1.

55. (AMENDED) The virus pseudo-nucleocapsid of claim 5, wherein said polynucleotide is [comprises a] from the group consisting essentially of hepatitis C virus genome and member of the *Flaviviridae* family.

60[61]. (AMENDED) The virus pseudo-nucleocapsid of claim 5, wherein said viral capsid polypeptide [virus pseudo-nucleocapsid] is formed by [cotransfecting] adding to a[n Sf-9 insect] cell-free in vitro system a [with] recombinant [baculovirus] DNA [and wild-type baculovirus DNA] consisting essentially of at least the first 124 amino-terminal residues of the hepatitis C virus core protein or a homologous sequence of a core protein from a member of the *Flaviviridae* family.